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Delirium severity in critical COVID-19 patients from an Infectious Disease Intensive Care Unit

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Highlights

- Neurological complications in COVID-19 have been described including delirium
- COVID-19 is not associated with higher prevalence or duration of delirium
- COVID-19 is associated with more severe forms of delirium

Title: Delirium severity in critical COVID-19 patients from an Infectious Disease Intensive Care Unit

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Declarations

This manuscript complies with all instructions to authors and final manuscript was approved by all authors.

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STROBE Checklist was used in this manuscript

This work adheres to ethical guidelines and the study has received ethical approval by the Ethics Committee of Centro Hospitalar Universitário São João.

As a retrospective study the informed consent is not applicable.

Contributorship:

Dr. Rafael Dias performed substantial contributions to the conception and design of the work, acquired relevant data and performed statistical analysis. Drafted the manuscript and revised it. Approved the final version of the manuscript to be published.

Dr. João Paulo Caldas performed substantial contributions to the conception of the work and acquired relevant data. Revised critically the manuscript with important intellectual content and approved the final version of the manuscript to be published.

Dr. André Silva-Pinto performed substantial contributions to the conception and design of the work and acquired relevant data. Revised critically the manuscript with important intellectual content and approved the final version of the manuscript to be published.

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Prof. Dr. Lurdes Santos performed substantial contributions to the conception and design of the work. Revised critically the manuscript with important intellectual content and approved the final version of the manuscript to be published.

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Dr. Rafael Dias, Dr. João Paulo Caldas, Dr. André Silva-Pinto, Dr. Andreia Costa, Prof. Dr. António Sarmento and Prof. Dr. Lurdes Santos have nothing to disclose.

Abstract

Background: COVID-19 is mainly characterized by respiratory manifestations. Nevertheless, neurological complications have been described including delirium, which appears to be frequent, prolonged, and severe.

Methods: Retrospective analysis of demographic, clinical and laboratory data of two cohorts: COVID-19 patients admitted to the infectious disease intensive care unit (ID-ICU) and patients admitted to the ID-ICU with other respiratory infections in 2018-2019. Outcomes were defined as presence, duration, and severity of delirium. Doses of antipsychotics used to control delirium were converted to equivalents and used as delirium severity. Logistics regression models were used to correlate COVID-19 with the outcomes.

Results: Ninety-nine COVID-19 patients and 40 non-Covid-19 patients were included. Mean age of COVID-19 cohort was 63 years-old with a male predominance. Delirium developed in 42%, with median duration of 3 days and equivalent dose of olanzapine used of 10mg/day.

In univariate analysis, COVID-19 was not associated with development or different duration of delirium when compared with non-COVID-19 patients. There was an association between COVID-19 and severity of delirium in a binary logistic regression model controlled to confounding variables.

Conclusion: COVID-19 is not associated with higher prevalence or duration of delirium compared to non-COVID-19 cohorts. However, it is associated with more severe forms.

Introduction:

SARS-CoV-2 cause potentially serious respiratory, gastrointestinal, neurological and/or liver disorders. The prevalence of neurological complications associated with SARS-CoV-2 infection varies according to the different series, with the most common manifestations being headache, anosmia and ageusia (Andreia Costa, 2020). Other complications include strokes, epilepsy, neuromuscular symptoms, and delirium (L. Mao et al., 2020; Zubair et al., 2020).

The mechanism by which the SARS-CoV2 virus produces nervous system symptoms is still unknown, but several mechanisms have been proposed including transsynaptic transfer between infected neurons, entry by the olfactory nerve, infection of the vascular endothelium or migration of infected leukocytes through the blood-brain barrier. (Zubair et al., 2020) More recently other hypothesis postulates an indirect damage of SARS-CoV2 to central nervous system due to low oxygen levels, coagulopathy, exposure to sedative and analgesic drugs, isolation, and immobility.(Pun et al., 2021)

It is estimated that about 20-40% of patients admitted to the Intensive Care Unit (ICU) develop delirium and the incidence may be higher in mechanical ventilated patients. In addition, the presence of delirium and its duration and severity are risk factors for long-term cognitive sequelae in patients who survive critical illnesses. (Salluh & Latronico, 2019) Delirium, reported in up to 84% of patients with COVID-19, can be associated with several mechanisms including direct infection and parenchymal injury, toxic-metabolic encephalopathy, epilepsy, or immune-mediated injury. However, cases of meningoencephalitis caused by SARS-CoV-2 are rare and more investigation is needed to clarify direct virus injury to the Central Nervous System (CNS)(Espíndola et al., 2020; J. Helms et al., 2020; Khan et al., 2020; L. Mao et al., 2020; Pun et al., 2021; Zubair et al., 2020)

We formulated the hypothesis that delirium in patients with COVID-19 is frequent, severe and may last over time. In addition, there is a lack of knowledge of the possible long-term effects of SARS-CoV2 on the central nervous system.

Thus, well-constructed, comparative studies are needed to understand the real extent and prognosis of delirium in COVID-19 patients.

Objectives

We aim to evaluate the prevalence of delirium, its characteristics, namely duration and severity in a cohort of critically ill COVID-19 patients, when compared with a cohort of critically ill patients admitted due to other respiratory infections.

Methods

Patient Selection

We performed a cohort study including two cohorts of COVID-19 and non-COVID-19 patients to compare similar patients who underwent similar practices on the same unit. We retrospectively analyzed all consecutive patients with respiratory symptoms and laboratory confirmed SARS-CoV-2 infection admitted to the Infectious Disease Intensive Care Unit (ID-ICU) of our Tertiary Center between March 2020 and December 2020 (COVID-19 patients), and we also reviewed all consecutive patients with clinically confirmed respiratory infection admitted to the ID-ICU between January 2018 and December 2019 (non-COVID-19 patients).

Patients were excluded if moribund (died in the first 24 hours after admission), those still under deep sedation when life-supporting measures were withdrawn and patients with no Acute Physiology and Chronic Health Evaluation (APACHE) score calculated. The study protocol was approved by the Local Ethics Committee.

Parameter Acquisition

We assessed electronic medical records and retrieved demographic and clinical variables such as sex, age, comorbidities including vascular risk factors, previous neuropsychiatric diseases that could impact the development of delirium including cognitive impairment, impairment of sensory inputs namely visual, auditory, olfactory, gustatory or tactile, previous cerebrovascular disease ou demyelinating disease, presence of epilepsy, and previously diagnosed psychiatric illness and chronic medication including previous use of benzodiazepines and antipsychotics. APACHE II

score, Simplified Acute Physiology Score (SAPS) II and III Score and organic disfunction at admission according to Marshall and Meakins criteria were retrieved as it could influence the delirium characteristics. We also reviewed length of stay in the ID-ICU, need and duration of endotracheal intubation (ETI), the usage of prone position and development of bacterial superinfection as the length of stay and these factors associated with increased length of stay could impact the development or duration of delirium.

Antipsychotics and benzodiazepines were registered and maximum daily dosages of antipsychotics used were converted to dose equivalents of olanzapine according to the International Consensus Study of Antipsychotic Dosing.(Gardner, Murphy, O'Donnell, Centorrino, & Baldessarini, 2010)

Outcome Measures

Outcome measures were defined as presence, duration, and severity of delirium. Development of delirium was assessed by revision of neurological status descriptions in electronic medical records. Although there are currently several bedside assessment scales validated for assessment of delirium, namely CAM-ICU, its implementation in our unit is still underway. Due to lack of CAM-ICU documentation on several patients from both cohorts, the presence of delirium was assessed only by recorded accurate daily descriptions of patients' mental status. Duration of delirium was defined by every day that the neurological status recorded on patients' charts was compatible with hypo or hyperactive delirium, namely impaired consciousness, disorientation, confusion, or agitation. Maximum daily dosages of antipsychotics used were converted to dose equivalents of olanzapine according to the International Consensus Study of Antipsychotic Dosing (Gardner et al., 2010) and used as a delirium severity marker. For accurate statistical analysis dose equivalents of olanzapine were also dichotomized into a nominal variable with a cut-off value of 10mg/day.

Statistical Analysis

We compared the baseline categorical and continuous independent variables between cohorts and between outcomes (developed delirium or not) with Chi-square test and Mann-Whitney test, according to variables characteristics and distribution. Possible confounders with a $p<0.1$ in univariable analysis and factors with plausibility to influence results were included in the multivariable model. We performed backward

elimination to identify independent predictors of the outcome. The effect of COVID-19 infection on defined outcomes was accessed using a binary logistics regression model, generating adjusted odds ratios (aOR) and 95% confidence intervals (CI). All statistical analyses were performed using IBM SPSS Statistics® version 26. Significance was set at $p<0.05$.

Results

From a total of 177 potential patients (128 COVID-19 patients and 49 non-COVID-19 patients), we excluded 38 patients due to the presence of at least one exclusion criteria. (Figure 1).

We included 139 patients (99 in the COVID-19 cohort and 40 in the non-COVID-19 cohort) in the final analysis. During COVID-19 pandemic our 6-bed intensive care unit was upgraded into a 10-bed intensive care unit to fully respond to the needs, which explains the disparity in total number of patients included in both cohorts.

The respiratory infectious agents identified in the 139 patients are shown in Table 1.

Both cohorts had few different characteristics (Table 2). COVID-19 patients were older, had less severe dysfunctions according to the defined severity admission scores (SAPSII, SAPSIII and APACHE), higher prevalence of vascular risk factors (hypertension, diabetes, dyslipidemia) although lower rates of smoking/ex-smoking habits) and fewer organ dysfunctions at admission (renal, cardiovascular, hematological, and neurological).

Co-morbidities were present in 90.9% of COVID-19 patients, of which 12% had previous neuropsychiatric disease including five mild cognitive impairment, two previous stroke, one epilepsy, one central demyelinating disease, one diabetic neuropathy, one toxic necrotizing myopathy, and one maniac depressive disorder. No patient had severe visual impairment. Only 2% and 26.3% of COVID-19 patients were previously taking antipsychotics and benzodiazepines, respectively.

Both cohorts presented similar frequency in the development of delirium: 42% in COVID-19 patients versus 58% in non-COVID-19 patients. Magnetic resonance imaging (MRI) or electroencephalography (EEG) were performed in 9 (5 COVID-19 patients) and 10 patients (5 COVID-19 patients) respectively. 1 EEG was considered normal (non-COVID-19 patient) and the other 9 showed diffuse slowing compatible

with unspecified encephalopathy. Only 1 MRI of the 5 COVID-19 patients showed a concomitant cerebral venous thrombosis, while the others lacked any concomitant cerebral insult. The duration of delirium was similar (3 to 4 days) (Table 3). The presence of COVID-19, previous neurological disease, antipsychotic use, or benzodiazepine use were not associated with development of delirium. However, there was a higher prevalence of male patients, auto-immune disease, higher severity scores at admission and cardiovascular, hematological, and neurological organic dysfunctions in the group that developed delirium. Patients that developed delirium also had longer ID-ICU stays, higher need of endotracheal intubation (ETI) and higher rates of bacterial superinfection. COVID-19 patients required a higher dose of antipsychotics to control delirium, with a median of 10.2mg/day vs 0.68mg/day (Table 4).

In univariate binary logistics regression analysis, male sex, higher APACHE score, cardiovascular and neurological dysfunction at admission, length of stay in ID-ICU, need for ETI and bacterial superinfection were the only risk factors for development of delirium. When adjusted for confounding variables only male sex (aOR 2.64, 95% CI 1.02-6.82, p=0.046) and need of ETI (aOR 10.3, 95% CI 3.69-29.0, p<0.001) presented as independent risk factors to the development of delirium (Table 5).

In univariate binary logistic regression analysis, the presence of COVID-19, was the only risk factor for the use of dosages of antipsychotics above 10mg/day used (p<0.05), however when adjusted for confounding variables we identified COVID-19 (aOR = 19.7, 95% CI 2.69-144.7, p<0.005) as well as length of stay in ID-ICU (aOR = 1.05, 95% CI 1.00-1.09, p<0.05) and male sex (aOR = 4.71, 95% CI 1.17-19.0, p<0.05) as independent risk factors for delirium severity (Table 6).

Discussion

We did not find that the presence of COVID-19 increase the risk of developing delirium, neither its duration. Nevertheless, the development of delirium in critically ill COVID-19 patients appears to be associated with much more severe manifestations with the need for higher dosages of antipsychotics to control the symptoms.

Acquired knowledge of SARS-CoV2 infection has shown that neurological symptoms could range from mild nonspecific or specific symptoms such as the loss of various

sensory perceptions, or more severe involvement. The mechanism of encephalopathy in COVID patients remains to be determined.(Jarrahi et al., 2020)

Delirium is extremely common in the intensive care unit (ICU) especially amongst mechanically ventilated patients. Different mechanisms have been proposed to explain delirium such as medication sedatives namely benzodiazepines, opiates, sepsis, respiratory disease, older age, previous alcohol abuse, previous psychiatry medication or underlying central nervous system disease.(Cavallazzi, Saad, & Marik, 2012)

Helms *et al.*, on a cohort of 58 ICU COVID-19 patients, reported that 84% developed neurological symptoms, of which 69% developed delirium and later a cohort of 150 ICU patients reported delirium and/or altered neurologic exam in 84% of patients, from whom 18% showed signs of delirium at ICU admission (Julie Helms et al., 2020; J. Helms et al., 2020).

The largest cohort study performed, with more than 2000 COVID-19 patients, reported the presence of acute brain dysfunction (coma or delirium) to be more common and more prolonged than in other studies of acute respiratory failure without COVID-19; prevalence of delirium was reported to be around 54% with a mean duration of 3 days when addressed through validated tools.(Pun et al., 2021)

Our study, although retrospective, shows a slightly lower prevalence of delirium (42%) with a duration of 3 days, consistent with other multicenter COVID-19 studies (J. Helms et al., 2020; Pun et al., 2021) improving the validity of our results. Albeit our study disclosed that delirium in COVID-19 patients is not more common or prolonged when compared to other respiratory failure patients admitted to the same unit with similar management protocols. The lower prevalence of delirium in COVID-19 patients could be because delirium screening was not performed systemically in our unit. Also due to the prolonged data collection period of approximately nine months, management practices for COVID-19 and its associated complications were improved according to the newest evidence which could have induced some variability into the analysis.

Although there was a similar prevalence of delirium in COVID-19 patients and in non-COVID-19 patients, the latter presented with significantly higher severity scores and organ dysfunction, known risk factors for the development of complications associated with prolonged ID-ICU stay and delirium.(Marra, Ely, Pandharipande, & Patel, 2017; Pun et al., 2019)

Patients with more severe disease and in need for a higher level of care appear to have a higher incidence of neurological complications (Ling Mao et al., 2020) including delirium, encephalopathy and signs of first neuron injury (Zubair et al., 2020), nevertheless it is still unknown if any of these complications are specific to COVID-19 and not just complications related to concomitant morbidities.

A recent study demonstrated that mechanical ventilation, use of restraints, benzodiazepine, opioid and vasopressor infusions, and antipsychotics were associated with a higher risk of delirium in the day after in COVID-19 patients (Pun et al., 2021).

In addition to the risk factors for delirium in the ICU and neuropathogenesis of SARS-CoV-2, the pandemic also created circumstances that further increase the risk of delirium, such as isolation of patients, absence of family visitors and the inability to freely ambulate.(Kotfis et al., 2020)

We also confirmed that male sex and need of ETI are independent predictors of development of delirium when adjusted for age, sex, length of ID-ICU stay, need of ETI and neurological dysfunction at admission. In accordance with a recent paper demonstrating female sex to be associated with more delirium and coma-free days, and invasive mechanical ventilation to be associated with higher risk of delirium the next day.(Pun et al., 2021) Furthermore COVID-19 mostly affects males, possibly due to the higher number of ACE2-expressing cells in their lungs (J. Helms et al., 2020).

COVID-19 infection, lengthier ID-ICU stay, male sex at admission were independent risk factors for severe delirium in the ICU when adjusted for age, sex, length of ID-ICU stay, need of ETI and neurological dysfunction at admission, consistent with recent reports showing severe delirium in COVID-19 patients(Khan et al., 2020)

Due to the retrospective design of our study, categorization of delirium type was not performed, and higher doses of antipsychotics used might suggest higher incidence of hyperactive delirium; published reports demonstrate different rates of delirium types in COVID-19 patients, either similar incidence of hypoactive and hyperactive or higher incidence of hypoactive delirium (Khan et al., 2020; Pun et al., 2021).

This study has several limitations. This is a single center study which decreases the external validity of our results. Due to the retrospective study design, assessment of delirium might be less sensitive. Also, the two cohorts had few baseline differences,

these were taken into consideration as confounding factors in the logistic regression model. Because the non-COVID-19 cohort was of 2018-2019, the presence of COVID-19 meant not only the presence of infection, but also all the measures implemented to "flatten the curve" including limited family visitors, worse non-verbal communication between health-care professionals and the patient due to the use of individual protective equipment. The use of antipsychotics drug as a surrogate marker of delirium severity may not show the full picture of the delirium. Though, the protocols for delirium management in the ID-UCI used were the same since 2018, demonstrating a similar approach in both cohorts. Due to the prolonged period of data collection (around 9 months), several practices in the routine care of COVID-19 patients were changed including postponing mechanical ventilation and routine use of videocalls to family members, that were implemented only after a few months of COVID-19 care.

To our knowledge this is the first study to compare delirium in two cohorts of COVID-19 patients and non-COVID-19 respiratory patients treated in the same unit over different but close time periods.

By demonstrating the presence of more severe delirium associated with COVID-19, it becomes clear the need for better interventions to minimize the development of delirium in these patients. Furthermore, the presence of severe hyperactive delirium in the context of a pandemic with over-crowded health-care services could theoretically lead to inter-hospital spread of the virus due to agitated uncooperative patients prior to intubation (Kotfis et al., 2020).

Despite the existence of the ABCDEF safety bundle to reduce the incidence of delirium and improve care of critically ill patients, a further analysis of existing guidelines is somewhat harder to accomplish in the middle of a pandemic scenario, requiring adaptations and modifications. Family involvement was perhaps the most neglected component during the pandemic, harder to accomplish at first, but as the pandemic progressed, newer techniques including videocalls, daily clinical updates from the medical team, and dedicated time to listen to family concerns and thoughts were a few solutions to keep the family involved in the caring of COVID-19 patients (Kotfis et al., 2020).

With the prevention and correct management of delirium in COVID-19 patients we are ensuring a better recovering and reducing the risk of long-term neurological complications of surviving patients.

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References

Andreia Costa, A. S.-P. (2020). <Neurological Manifestations and COVID-19.pdf>. *Acta Médica Portuguesa, 33*(12).

Cavallazzi, R., Saad, M., & Marik, P. E. (2012). Delirium in the ICU: an overview. *Annals of Intensive Care, 2*(1), 49. doi:10.1186/2110-5820-2-49

Espíndola, O. M., Siqueira, M., Soares, C. N., Lima, M., Leite, A., Araujo, A. Q. C., . . . Silva, M. T. T. (2020). Patients with COVID-19 and neurological manifestations show undetectable SARS-CoV-2 RNA levels in the cerebrospinal fluid. *Int J Infect Dis, 96*, 567-569. doi:10.1016/j.ijid.2020.05.123

Gardner, D. M., Murphy, A. L., O'Donnell, H., Centorrino, F., & Baldessarini, R. J. (2010). International consensus study of antipsychotic dosing. *Am J Psychiatry, 167*(6), 686-693. doi:10.1176/appi.ajp.2009.09060802

Helms, J., Kremer, S., Merdji, H., Clere-Jehl, R., Schenck, M., Kummerlen, C., . . . Meziani, F. (2020). Neurologic Features in Severe SARS-CoV-2 Infection. *New England Journal of Medicine, 382*(23), 2268-2270. doi:10.1056/NEJMc2008597

Helms, J., Kremer, S., Merdji, H., Schenck, M., Severac, F., Clere-Jehl, R., . . . Meziani, F. (2020). Delirium and encephalopathy in severe COVID-19: a cohort analysis of ICU patients. *Crit Care, 24*(1), 491. doi:10.1186/s13054-020-03200-1

Jarrahi, A., Ahluwalia, M., Khodadadi, H., da Silva Lopes Salles, E., Kolhe, R., Hess, D. C., . . . Dhandapani, K. M. (2020). Neurological consequences of COVID-19: what have we learned and where do we go from here? *Journal of Neuroinflammation, 17*(1), 286. doi:10.1186/s12974-020-01957-4

Khan, S. H., Lindroth, H., Perkins, A. J., Jamil, Y., Wang, S., Roberts, S., . . . Khan, B. A. (2020). Delirium Incidence, Duration, and Severity in Critically Ill Patients With Coronavirus Disease 2019. *Crit Care Explor, 2*(12), e0290. doi:10.1097/cce.0000000000000290

Kotfis, K., Williams Roberson, S., Wilson, J. E., Dabrowski, W., Pun, B. T., & Ely, E. W. (2020). COVID-19: ICU delirium management during SARS-CoV-2 pandemic. *Crit Care, 24*(1), 176. doi:10.1186/s13054-020-02882-x

Mao, L., Jin, H., Wang, M., Hu, Y., Chen, S., He, Q., . . . Hu, B. (2020). Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China. *JAMA Neurol, 77*(6), 1-9. doi:10.1001/jamaneurol.2020.1127

Mao, L., Jin, H., Wang, M., Hu, Y., Chen, S., He, Q., . . . Hu, B. (2020). Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China. *JAMA Neurology, 77*(6), 683-690. doi:10.1001/jamaneurol.2020.1127

Marra, A., Ely, E. W., Pandharipande, P. P., & Patel, M. B. (2017). The ABCDEF Bundle in Critical Care. *Crit Care Clin, 33*(2), 225-243. doi:10.1016/j.ccc.2016.12.005

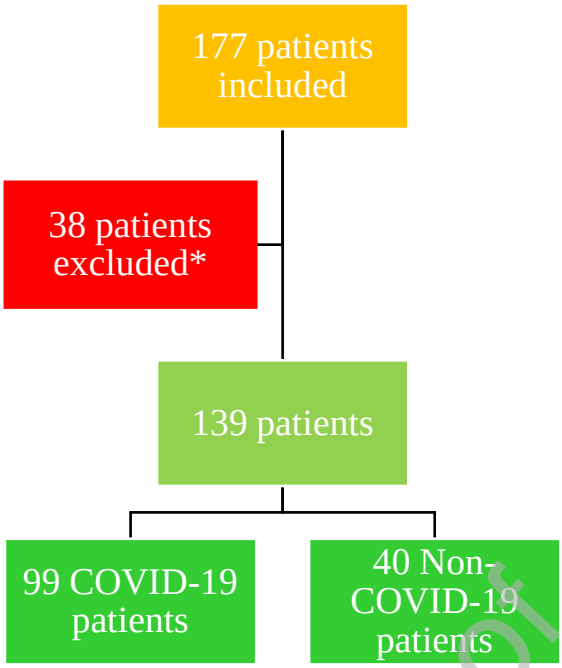
Pun, B. T., Badenes, R., Heras La Calle, G., Orun, O. M., Chen, W., Raman, R., . . . Pandharipande, P. P. (2021). Prevalence and risk factors for delirium in critically ill patients with COVID-19 (COVID-D): a multicentre cohort study. *Lancet Respir Med*. doi:10.1016/s2213-2600(20)30552-x

Pun, B. T., Balas, M. C., Barnes-Daly, M. A., Thompson, J. L., Aldrich, J. M., Barr, J., . . . Ely, E. W. (2019). Caring for Critically Ill Patients with the ABCDEF Bundle: Results of the ICU Liberation Collaborative in Over 15,000 Adults. *Crit Care Med, 47*(1), 3-14. doi:10.1097/ccm.0000000000003482

Salluh, J. I. F., & Latronico, N. (2019). Does this critically ill patient with delirium require any drug treatment? *Intensive Care Med, 45*(4), 501-504. doi:10.1007/s00134-018-5310-x

Zubair, A. S., McAlpine, L. S., Gardin, T., Farhadian, S., Kuruvilla, D. E., & Spudich, S. (2020). Neuropathogenesis and Neurologic Manifestations of the Coronaviruses in the Age of Coronavirus Disease 2019: A Review. *JAMA Neurology, 77*(8), 1018-1027. doi:10.1001/jamaneurol.2020.2065

Figure 1 – Decision tree for included patients



*Moribund (died in the first 24 hours after admission), still under deep sedation when life-supporting measures were withdrawn or with no Acute Physiology and Chronic Health Evaluation (APACHE) score calculated.

Table 1 Infectious respiratory agent

Infectious Agent	Frequency N=139 (100)
SARS-CoV-2	99 (71.2)
Pneumocystis jirovecii	1 (0.7)
Legionella	2 (1.4)
Streptococcus pneumoniae	8 (5.8)
Influenza A	7 (5.0)
Influenza B	1 (0.7)
Staphylococcus aureus	1 (0.7)
Cytomegalovirus	2 (1.4)
Leishmania	2 (1.4)
Not Identified	16 (11.5)

SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2

Table 2 Baseline characteristics of all patients and comparison between cohorts.

Variables	COVID-19 Cohort (n=99)	Non-COVID-19 Cohort (n=40)	P-value
Age, in years – Mean (SD)	63 (18)	57 (22)	0.020*
Male – n (%)	60 (60.6)	21 (52.5)	0.380
Comorbidities – n (%)	90 (90.9)	34 (85.0)	0.309
Hypertension – n (%)	57 (57.6)	15 (37.5)	0.032*
Diabetes Mellitus – n (%)	36 (36.4)	7 (17.5)	0.029*
Dyslipidemia – n (%)	50 (51.5)	12 (30.0)	0.021*
Chronic Cardiac Disease – n (%)	19 (19.2)	4 (10.0)	0.187
Smoker/Ex-Smoker – n (%)	14 (14.1)	17 (42.5)	0.001**
Alcohol Abuse – n (%)	6 (6.1)	6 (15.0)	0.089
Asthma – n (%)	2 (2.0)	1 (2.5)	0.860
COPD – n (%)	6 (6.1)	6 (15.0)	0.089
OSAS – n (%)	7 (7.1)	0 (0)	0.084
Liver Chronic Disease – n (%)	7 (7.1)	6 (15.0)	0.146
Renal Chronic Disease – n (%)	7 (7.2)	6 (15.0)	0.146
Chronic Hematogenous Disease – n (%)	3 (3.0)	1 (2.5)	0.866
Previous Neurological Disease – n (%)	12 (12.1)	6 (15.0)	0.647
Active Neoplasia – n (%)	8 (8.1)	4 (10.0)	0.715
HIV Infection – n (%)	1 (1.0)	6 (15.0)	0.001**
Previous Transplantation – n (%)	4 (4.0)	2 (5.0)	0.801
Auto-immune Disease – n (%)	6 (6.1)	3 (7.5)	0.766
Previous antipsychotic use – n (%)	2 (2.0)	2 (5.0)	0.341
Previous Benzodiazepines use – n (%)	26 (26.3)	9 (22.5)	0.644
APACHE Score – Mean (SD)	16 (5)	22 (8)	<0.001**
SAPSII Score – Mean (SD)	31 (14)	46 (17)	<0.001**
SAPSIII Score – Mean (SD)	51 (14)	66 (14)	<0.001**
Respiratory Dysfunction – n (%)	90 (90.1)	38 (95.0)	0.419
Renal Dysfunction – n (%)	15 (15.2)	15 (37.5)	0.004**
Cardiovascular Dysfunction – n (%)	23 (23.2)	21 (52.5)	0.001**
Hematological Dysfunction – n (%)	13 (13.1)	13 (32.5)	0.008**
Neurological Dysfunction – n (%)	10 (10.1)	15 (37.5)	<0.001**
Liver Dysfunction – n (%)	15 (15.2)	8 (20.0)	0.486
Length of stay IDICU, in days – median (IQR)	8 (16)	12 (23)	0.019**
Need of ETI – n (%)	42 (42.4)	26 (65.0)	0.016**
Length of ETI use, in days – median (IQR)	13 (12)	12 (16)	0.749
Prone position used – n (%)	42 (42.4)	9 (22.5)	0.014**
Bacterial superinfection – n (%)	34 (34.3)	10 (25.0)	0.284
Development of Delirium – n (%)	42 (42.4)	23 (58)	0.107

COPD - Chronic obstructive pulmonary Disease; OSAS – Obstructive sleep apnea syndrome; HIV – Human immunodeficiency virus; APACHE - Acute Physiology and Chronic Health Evaluation (APACHE) II score; SAPSII- Simplified Acute Physiology Score; IDICU – Infectious diseases intensive care unit; ETI-Endotracheal Intubation

*p-value<0.05

**p-value<0.005

Table 3 Baseline characteristics of patients with and without delirium

	Development of Delirium		
Variables	Yes (N=65)	No (N=74)	P-value
Age, in years – Mean (SD)	63 (16)	61 (15)	0.154
Male – n (%)	44 (67.7)	37 (50.0)	0.035*
Comorbidities – n (%)	59 (90.8)	65 (87.8)	0.578
Hypertension – n (%)	39 (60.0)	33 (44.6)	0.070
Diabetes Mellitus – n (%)	22 (33.8)	21 (28.4)	0.487
Dyslipidemia – n (%)	32 (49.2)	31 (41.9)	0.386
Chronic Cardiac Disease – n (%)	14 (21.5)	9 (12.2)	0.138
Smoker/Ex-Smoker – n (%)	18 (27.7)	13 (17.6)	0.152
Alcohol Abuse – n (%)	8 (12.3)	4 (5.4)	0.148
Asthma – n (%)	1 (1.5)	2 (2.7)	0.637
COPD – n (%)	7 (10.8)	5 (6.8)	0.401
OSAS – n (%)	5 (7.7)	2 (2.7)	0.180
Liver Chronic Disease – n (%)	8 (12.3)	5 (6.8)	0.262
Renal Chronic Disease – n (%)	7 (10.8)	6 (8.1)	0.591
Chronic Hematogenous Disease – n (%)	2 (3.1)	2 (2.7)	0.895
Previous Neurological Disease – n (%)	11 (16.9)	7 (9.5)	0.191
Active Neoplasia – n (%)	4 (6.2)	8 (10.8)	0.329
HIV Infection – n (%)	2 (3.1)	5 (6.8)	0.322
Previous Transplantation – n (%)	3 (4.6)	3 (4.1)	0.871
Auto-immune Disease – n (%)	1 (1.5)	8 (10.8)	0.028*
Previous antipsychotic use – n (%)	3 (4.6)	1 (1.4)	0.251
Previous Benzodiazepines use – n (%)	19 (29.2)	16 (21.6)	0.302
COVID-19 infection – n (%)	42 (64.6)	57 (77.0)	0.107
APACHE Score – Mean (SD)	20 (6)	16 (6)	0.001**
SAPSII Score – Mean (SD)	40 (16)	32 (16)	0.003**
SAPSIII Score – Mean (SD)	60 (15)	51 (15)	0.001**
Respiratory Dysfunction – n (%)	61 (93.8)	67 (90.5)	0.471
Renal Dysfunction – n (%)	18 (27.7)	12 (16.2)	0.101

Cardiovascular Dysfunction – n (%)	33 (50.8)	11 (14.9)	<0.001**
Hematological Dysfunction – n (%)	17 (26.2)	9 (12.2)	0.035*
Neurological Dysfunction – n (%)	20 (30.8)	5 (6.8)	<0.001**
Liver Dysfunction – n (%)	12 (18.5)	11 (14.9)	0.569
Length of stay ID-ICU – median (IQR)	19 (19)	6 (6)	<0.001**
Need of ETI – n (%)	53 (81.5)	15 (20.3)	<0.001**
Length of ETI use – median (IQR)	16 (13)	8 (14)	0.197
Prone position used – n (%)	26 (40.0)	25 (33.8)	0.426
Bacterial superinfection – n (%)	31 (47.7)	13 (17.6)	<0.001**

COPD - Chronic obstructive pulmonary Disease; OSAS – Obstructive sleep apnea syndrome; HIV – Human immunodeficiency virus; APACHE - Acute Physiology and Chronic Health Evaluation (APACHE) II score; SAPSII- Simplified Acute Physiology Score; ID-ICU – Infectious diseases intensive care unit; ETI-Endotracheal Intubation

*p-value<0.05

**p-value<0.005

Table 4 Comparison between COVID-19 and non-COVID-19 patients with delirium

	Patients with delirium (n=65)		
Variables	COVID-19 Cohort (n=42)	Non-COVID-19 Cohort (n=23)	P-value
Age, in years – Mean (SD)	67 (14)	57 (16)	0.018*
Male – n (%)	30 (71.4)	14 (60.9)	0.384
Comorbidities – n (%)	40 (95.2)	19 (82.6)	0.093
Hypertension – n (%)	29 (69.0)	10 (43.5)	0.044*
Diabetes Mellitus – n (%)	17 (40.5)	5 (21.7)	0.127
Dyslipidemia – n (%)	25 (59.5)	7 (30.4)	0.025*
Chronic Cardiac Disease – n (%)	11 (26.2)	3 (13.0)	0.218
Smoker/Ex-Smoker – n (%)	8 (19.0)	10 (43.5)	0.035*
Alcohol Abuse – n (%)	3 (7.1)	5 (21.7)	0.087
Asthma – n (%)	1 (2.4)	0 (0)	0.456
COPD – n (%)	3 (7.1)	4 (17.4)	0.202
OSAS – n (%)	5 (11.9)	0 (0)	0.085
Liver Chronic Disease – n (%)	5 (11.9)	3 (13.0)	0.894
Renal Chronic Disease – n (%)	2 (4.8)	5 (21.7)	0.035*
Chronic Hematogenous Disease – n (%)	2 (4.8)	0 (0)	0.288
Previous Neurological Disease – n (%)	5 (11.9)	6 (26.1)	0.145
Active Neoplasia – n (%)	3 (7.1)	1 (4.3)	0.654
HIV Infection – n (%)	0 (0)	2 (8.7)	0.052
Previous Transplantation – n (%)	1 (2.4)	2 (8.7)	0.246
Auto-immune Disease – n (%)	1 (2.4)	1 (4.3)	0.178
Previous antipsychotic use – n (%)	1 (2.4)	2 (8.7)	0.246
Previous Benzodiazepines use – n	13 (31.0)	6 (26.1)	0.680

(%)			
APACHE Score – Mean (SD)	18 (5)	24 (6)	<0.001**
SAPSII Score – Mean (SD)	34 (14)	50 (14)	<0.001**
SAPSIII Score – Mean (SD)	54 (15)	70 (11)	<0.001**
Respiratory Dysfunction – n (%)	39 (92.9)	22 (95.7)	0.654
Renal Dysfunction – n (%)	9 (21.4)	9 (39.1)	0.127
Cardiovascular Dysfunction – n (%)	17 (40.5)	16 (69.6)	0.025*
Hematological Dysfunction – n (%)	9 (21.4)	8 (34.8)	0.241
Neurological Dysfunction – n (%)	9 (21.4)	11 (47.8)	0.027*
Liver Dysfunction – n (%)	8 (19.0)	4 (17.4)	0.869
Length of stay ICUID – median (IQR)	18 (19)	20 (24)	0.269
Need of ETI – n (%)	32 (76.2)	21 (91.3)	0.133
Length of ETI use – median (IQR)	13 (11)	12 (16)	0.815
Prone position used – n (%)	20 (47.6)	6 (26.1)	0.052
Bacterial superinfection – n (%)	23 (54.8)	8 (34.8)	0.123
Delirium Duration – median (IQR)	3 (5)	4 (2)	0.702
Antipsychotic equivalent dose, in mg/day – median (IQR)	10.3 (17)	0.68 (10)	0.034*

COPD - Chronic obstructive pulmonary Disease; OSAS – Obstructive sleep apnea syndrome; HIV – Human immunodeficiency virus; APACHE - Acute Physiology and Chronic Health Evaluation (APACHE) II score; SAPSII- Simplified Acute Physiology Score; IDICU – Infectious diseases intensive care unit; ETI-Endotracheal Intubation

*p-value<0.05

**p-value<0.005

Table 5 Prediction of development of delirium by logistic regression analysis

	Development of Delirium	Univariate Analysis	Multivariate Analysis[a]	
Variables	Yes (N=65)	No (N=74)	OR (CI)	aOR (CI)
Age, in years – Mean (SD)	63 (16)	61 (15)	1.02 (0.99-1.04)	1.02 (0.99-1.06)
Male – n (%)	44 (67.7)	37 (50.0)	2.10 (1.05-4.18)*	2.64 (1.02-6.82)*
APACHE Score – Mean (SD)	20 (6)	16 (6)	1.10 (1.03-1.16)**	0.99 (0.92-1.06)
COVID-19 infection – n (%)	42 (64.6)	57 (77.0)	0.55 (0.26-1.15)	1.04 (0.35-3.14)
Cardiovascular Dysfunction – n (%)	33 (50.8)	11 (14.9)	5.91 (2.64-13.2)**	1.11 (0.35-3.49)

Neurological Dysfunction – n (%)	20 (30.8)	5 (6.8)	6.13 (2.15-17.5)**	3.65 (0.89-14.9)
Length of stay ID-ICU – median (IQR)	19 (19)	6 (6)	1.10 (1.06-1.15)**	1.04 (1.00-1.09)
Need of ETI – n (%)	53 (81.5)	15 (20.3)	17.4 (7.46-40.4)**	10.3 (3.69-29.0)**
Bacterial superinfection – n (%)	31 (47.7)	13 (17.6)	4.28 (1.98-9.26)**	1.22 (0.39-3.82)

APACHE - Acute Physiology and Chronic Health Evaluation (APACHE) II score; IDICU – Infectious diseases intensive care unit; ETI-Endotracheal Intubation

[a]Adjusted for age, sex, Length of ID-ICU Stay, Need of ETI, Neurological dysfunction

*p-Value <0.05;

**p-Value <0.005; OR=Odds Ratio; aOR=adjusted Odds Ratio; CI=Confidence Interval

Table 6 Prediction of Antipsychotic dose equivalent in patients who developed delirium, by logistic regression analysis.

	Antipsychotic dose equivalent > 10mg/day in patients who developed delirium	Univariate Analysis	Multivariate Analysis[a]	
Variables	Yes (N=25)	No (N=40)	OR (CI)	aOR (CI)
Age, in years – Mean (SD)	64 (16)	63 (16)	1.00 (0.97-1.04)	1.02 (0.98-1.06)
Male – n (%)	20 (80)	25 (60)	2.67 (0.83-8.56)	4.71 (1.17-19.0)*
APACHE Score – Mean (SD)	19 (5)	21 (7)	0.94 (0.86-1.02)	0.90 (0.81-1.00)*
COVID-19 infection – n (%)	21 (84)	21 (52.5)	4.75 (1.38-16.4)*	19.7 (2.69-144.7)**
Cardiovascular Dysfunction – n (%)	13 (52)	20 (50)	1.08 (0.40-2.94)	0.75 (0.23-2.45)
Neurological Dysfunction – n (%)	10 (40)	10 (25)	2.00 (0.68-5.85)	1.64 (0.52-5.16)
Length of stay ID-ICU – median (IQR)	22 (17)	15 (21)	1.02 (0.99-1.06)	1.05 (1.00-1.09)*
Need of ETI – n (%)	21 (84)	32 (80)	1.31 (0.35-4.92)	0.71 (0.16-3.19)
Bacterial superinfection – n (%)	15 (60)	16 (40)	2.25 (0.81-6.24)	1.89 (0.53-

				6.80)

APACHE - Acute Physiology and Chronic Health Evaluation (APACHE) II score; IDICU – Infectious diseases intensive care unit; ETI-Endotracheal Intubation

[a]Adjusted for age, sex, Length of IDICU Stay, Need of ETI, Neurological dysfunction

[*]p-Value <0.05;

[**]p-Value <0.005; OR=Odds Ratio; aOR=adjusted Odds Ratio; CI=Confidence Interval